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Walking the Talk: Doing Science with Perimenopausal Women and their Health Care Providers

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Introduction

We will examine the unique interconnectedness of research and practice in relationship to perimenopause (women's normal life phase that is the transition between reproductive adulthood and menopause). This introduction will provide an annotated narrative of the personal and medical-political aspects of our discovery that perimenopause is a time of high and chaotic estrogen levels, rather than declining levels, as the current paradigm insists. That story will be followed by two aspects of the pilot research we began in an effort to transform knowledge into something that would assist those clinicians seeing distressed women and feeling at a loss to help them to understand and deal with a difficult time in perimenopause.

The story begins when the first author began to wake at night sweating and remain sleepless, had continuous sore and swollen breasts and dreamed that she was pregnant (Prior, 1998a). As a medical specialist in endocrinology, she knew that her symptoms *could not* be caused by low estrogen levels. She, like other physicians, had been taught that dropping estrogen levels occurred before menopause (one year without a period). She became angry that the "received wisdom" was opposite to her experience—she knew that she, like many women she had struggled to treat, was face to face with *higher* estradiol levels.

These strong feelings motivated the first author to carefully and systematically explore the medical literature related to the hormonal and experience changes of perimenopause (Prior, 1998b). A meta-analysis of published studies that compared, within centre, premenopausal and perimenopausal women's serum estradiol levels showed average levels 30 percent higher than in younger women (Prior, 1998b).

Meanwhile, the hypothesis that estrogen levels are declining in perimenopause (Burger et al., 1995) was sufficiently strong that seasoned clinical investigators could not "see" the very high estradiol levels that they, themselves, documented in an excellent population-based study (Prior, Barr, & Vigna, 1996). A further review by the first author documented clearly that ovulation disturbances and lower progesterone levels are also common in perimenopause (Prior, 2002). Finally, in perimenopause, estrogen levels are not subject to the usual feedback controls and therefore are unlikely to be suppressible with estrogen therapy (Prior, 1998b). Because progesterone physiologically counterbalances the effects of estrogen, these hormonal changes of perimenopause suggested to us that progesterone, rather than estrogen, would be an appropriate therapy for symptomatic perimenopausal women.

A further practical problem for health care providers (HCP) and patients relates to the diagnosis of perimenopause. The higher estrogen and lower progesterone levels in midlife women occur when they are still cycling regularly (Santoro, Rosenberg, Adel, & Skurnick, 1996) and would therefore not yet meet the irregular-cycle criterion for entering the "menopausal transition" (the official name for perimenopause) (Soules et al., 2001). Irregular cycles are known to begin, on average, at 47.5 years in the population (McKinlay, Brambilla, & Posner, 1992) .

A further literature review documented a number of troublesome experiences associated with perimenopause—heavy flow, cyclic night sweats, sore breasts, mood swings, fluid retention, weight gain and sleep disturbances (Prior, 1998b). We followed this with analysis of Daily Perimenopause Diary© records showing that cyclic night sweats and breast tenderness occurred in regularly menstruating midlife women (Hale, Hitchcock, Williams, Vigna, & Prior, 2003). Reasons for most of these perimenopause-associated symptoms remain poorly understood, but abnormally heavy menstrual flow is caused by higher estrogen levels and lower progesterone effects (Moen, Kahn, Bjerve, & Halvorsen, 2004).

The conflict of new knowledge with an existing paradigm is common in science (Kuhn, 1970). Therefore the contentious issue about whether estrogen is high or dropping in perimenopause could be dismissed as an intellectual argument, or as an irrelevant conflict between physician/scientists working from different perspectives (Prior, 2005). However, as a group of women researchers, we could see the relevance of this new

science to the health and well-being of midlife women. This is especially so because the current therapy recommendations for symptomatic midlife women are estrogen therapy or oral contraceptives (containing supraphysiological estrogen levels even though they, with respect to the earlier Pill, are called "low dose") (Greendale & Greendale, 2002).

Our goal now became to develop safe and effective education and treatment for the approximately 20 percent of women who are symptomatic in perimenopause (Kaufert, Gilbert, & Hassard, 1988). Despite the current baby boom demographic, no perimenopausal therapies have been proven effective in randomized, double-blind, placebo-controlled trials. Low dose oral contraceptives (OC) make unexpected bleeding worse for the first three cycles and only in the fourth through the sixth cycles do they help reduce bleeding for perimenopausal women with heavy flow (Casper, Dodin, Reid, & Study Investigators, 1997). Furthermore, OC therapy did not significantly improve quality of life nor hot flushes compared with placebo (Casper et al., 1997). We know of no randomized controlled trials showing that estrogen/progestin is effective for hot flushes in perimenopausal as opposed to menopausal women.

Based on this new knowledge of the physiology of perimenopause (Prior, 1998b), we designed a placebo-controlled study comparing the recommended therapy, low dose OC, against progesterone therapy prescribed for the last 14 days of the menstrual cycle. We designed the progesterone therapy to be in a physiological dose (300 mg) that keeps the serum progesterone level in the luteal phase range for 24 hours since it can only be given at bedtime because of its sleep side effects (Friess, Tagaya, Trachsel, Holsboer, & Rupprecht, 1997). This would amount to "luteal phase replacement therapy," for those with anovulatory cycles. It would also supplement normal levels of progesterone to counterbalance the effects of the high estrogen levels or would augment short luteal phases if these were present.

We wrote and submitted a proposal for a double-blind, placebo-controlled randomized controlled three-arm study (low dose oral contraceptive, cyclic progesterone therapy, double placebo) for symptomatic women in early perimenopause. The trial was to last three years. We included a placebo arm, not just because this is the ideal trial design, but also because the natural history of experiences and symptoms was not known. We submitted our proposal to a Women's Health competition funded by a Medical Research Council of Canada-Industry Liaison grant. It was rejected with comments that

OC had been proven successful in treatment of symptomatic perimenopause and that we were wrong about that study (Casper et al., 1997). We revised our proposal according to reviewers' comments and resubmitted the proposal to the Canadian Institutes of Health Research. With our second rejection that contained similar content concerns plus technical randomized controlled trial design corrections, we revised again and re-submitted. The third rejection, that received an even lower score than the first, caused us to give up trying. With the wisdom of hindsight, it is clear that the content reviewers of our grant proposal believed that the OC trial in perimenopause was successful (Casper et al., 1997). They held this understanding because of their hypothesis about perimenopause-as-dropping-estrogen and also because the pharmaceutical company sponsoring the trial and analyzing the trial data was not forced by the publishing journal nor the reviewers to state the statistical results of OC versus placebo in the abstract. Furthermore, figures in the published paper suggested that OC had beneficial effects although statistical significance was not met (Rowe & Allen, 2006; Casper et al., 1997).

The historical, demographic context in which we were making these observations and getting these rejected research applications was highly relevant to us. In 2000, approximately 19 percent of Canadian women were ages 40-55 and thus likely in perimenopause. We knew that 20 percent of perimenopausal women were symptomatic (Kaufert et al., 1988). We also knew that the hysterectomy rate in British Columbia was 4.1/1000 adult women/year—it varied from 2.4 in the metropolitan region with a medical school, to 6.7/1000/yr in a remote, rural region of the province (Ministry of Health, Ministry Responsible for Seniors, & Women's Health Bureau, 2000). The vast majority of hysterectomies are known to be performed for benign conditions (Maresh et al., 2002) and the average age at hysterectomy is between ages 44-46. This is before irregular cycles usually begin and thus before a diagnosis of perimenopause is made by conventional criteria (Soules et al., 2001)—women with hysterectomy would thus have no explanation for heavy flow and major surgery.

As women who were known in the region for our research and teaching about perimenopause and women's health, we were personally confronted with the legitimate and often urgent concerns of midlife women. They e-mailed, telephoned and faxed their questions and requests; about 10 women per week asked for our advice and help. We struggled to respond. Although, for the previous decade, the first author had been referred

and provided consultation care for the most symptomatic midlife women in the province, around this time, increasing academic demands caused her to close her one-day-a-week clinical practice to new patients.

In 2002 we founded the Centre for Menstrual Cycle and Ovulation Research and, in 2003 launched the CeMCOR Web site (www.cemcor.ubc.ca). Some of the first articles we posted there gave information about and self-help tools to aid perimenopausal women and their health care providers. This helped to relieve the responsibility to provide personal information for symptomatic perimenopausal women, but we were left with no scientific data on which to base our recommendations. We therefore decided to do a more practice-based investigation. We planned a long-distance consultation for women that would assist HCP to provide appropriate local care. We were already in touch with the James Bay Community Project in a city of about 100,000 located approximately three hours away by road and ferry. The Project was trying to start a midlife women's health programme as part of their medical clinic and asked for our support and advice. (This midlife programme never materialized for irrelevant reasons.) Therefore we began a pilot project that would at the same time be a long distance physician specialist consultation to HCP and also provide direct education and support for perimenopausal women.

We realized that we currently lacked data on the demographic, social, physical and medical characteristics of symptomatic women seeking assistance from their HCP about perimenopause, and that accurate information, support and learning to keep self-records would assist such women. We also needed to know what concerns HCP may have about their own assessment and management of symptomatic midlife women. Finally, we didn't know whether a specialist consultation for a specific patient would assist that HCP and, in turn, provide better care for his/her symptomatic perimenopausal patients.

Having described the course of this research from personal experience to new knowledge, to a venture into clinical practice research, the next two parts of this study will describe our preliminary research.

Part 1: Health Care Providers' Perceived Perimenopausal Management Problems

Primary health care providers (HCP) are nurse clinicians, general practitioners or family physicians that deliver primary medical care. There has long been considerable uncertainty about therapy for midlife women (Hemminki, Topo, Malin, & Kangas, 1993;

Barlow, Brockie, & Rees, 1991; Larcos, 1996) that consensus statements have unsuccessfully attempted to alleviate (Wathen, Feig, Feightner, Abramson, & Cheung, 2004). Because perimenopausal women are commonly called (and call themselves) "menopausal," and are understood to have dropping or low estrogen levels, they, like women one year beyond the final period (who are truly menopausal), are commonly treated with "estrogen replacement." Concerns about such treatment increased following publication of the results showing more harm than benefit from randomized controlled trials of hormone therapy in asymptomatic menopausal women (Writing Group for the Women's Health Initiative Investigators, 2002; Anderson et al., 2004). Would the results apply to perimenopause? The purpose of this HCP survey was to learn what concerns and symptoms midlife women brought that these professionals found most difficult to address.

Methods

A clinical scientist interviewed 30 different HCP (29 family or general physicians and one nurse clinician) in person or over the telephone. HCP were a convenience sample from two urban areas in coastal southern British Columbia. Sixteen HCP from one city had referred symptomatic perimenopausal women to the Pilot Perimenopause Experiences Project (Part 2). The remaining HCP from the larger city had referred patients to a single specialist within the preceding year. No consenting HCP was excluded; all available interview data were analyzed. HCP gave informed consent to this study that was approved by the Behavioural Research Ethics Board of the University of British Columbia.

The interview consisted of an open-ended question: "What kinds of problems or concerns do your midlife/perimenopausal women patients have that currently pose the most difficulty for you?" All answers were written on a research form verbatim. Sixteen of the HCP were asked the same question in a second interview an average of 11 weeks later to assess test-retest reliability of their responses.

We used descriptive statistics to analyze the interview responses of the HCP. For the purpose of analysis, the thirty-two test-retest interviews from the 16 HCP who were interviewed twice were each considered as separate interviews in tabulating the frequency of HCP perimenopausal concerns—this gave us a total of 46 interviews in the

30 HCP. Three independent scientists (two with an M.D. and one with a Ph.D.) reviewed these responses and grouped them into categories. These three sets of categories were then compared and sixteen domains identified. Differences were resolved by consensus resulting in eleven categories. Test-retest responses for the 16 physicians were analyzed using these 11 categories. Further, the gender of the HCP was evaluated for differences in frequency of categories by gender.

Results

HCP included 16 women and 14 men equally distributed between the two cities. The midlife/perimenopausal "problems or concerns" they identified were highly varied and, in their own words, included the following: "difficulty coping," "a lot of depression," "periods going wacky," "trouble coping with stress," "not responding to hormones," "anxiety about bone," "mood swings," "hot flushes/night sweats," "sleep disturbances," "sexual dysfunction," "anxiety," "questions about hormone therapy," and "osteoporosis." The eleven condensed categories are shown in Table 11. A frequency distribution of these categories is illustrated in Figure 11. Seventy-six percent of HCP interviews mentioned mood symptoms; over half suggested problems treating hot flushes and night sweats in midlife women, and about half reported sleep problems. Over 45 percent of HCP interviews mentioned that questions about when to use hormone therapy were problematic for them. Menstrual cycle problems such as menorrhagia were difficult for only 30 percent, and high estrogen symptoms were reported as problematic for only 18 percent.

The test-retest interviews were conducted with 16 HCP an average of 11 (range five to 16) weeks apart. Results (Table 21) showed that a quarter of the repeat interviews included none of the initial concerns of that HCP. Another quarter repeated only one previously mentioned concern, and 44 percent mentioned two of the same categories of concern at both interviews.

Gender was equally balanced among the HCP; and men and women contributed equally to the majority of the 11 domains of perimenopausal concerns (for example, 88 percent of women and 86 percent of men mentioned mood swings). However, 75 percent of women, but only 36 percent of men HCP identified vasomotor symptoms as problematic. Management of sleep disturbances among perimenopausal women likewise

concerned 63 percent of the women but only 36 percent of men HCP. These gender-related differences, although probably important, did not reach statistical significance in this small sample.

Discussion

Results of this small survey of HCP perimenopausal management concerns show 11 domains that they find difficult. The most prominent HCP concern was emotional lability (mood swings) that others have found to be prominent in symptomatic women ages 40-55 who visit their general practitioner (Barlow et al., 1991). "Psychogenic symptoms," however, had a frequency of only 2.3 percent in the wider clinical practice population of women ages 40-69 who were not seeing their physician with perimenopausal or menopausal concerns (Barlow et al., 1991).

Vasomotor symptoms (VMS) were also a common HCP concern. Because most HCP believe that low estrogen levels cause VMS, their occurrence in menstruating women was confusing. Although oral estrogen is highly effective for VMS in menopausal women based on a meta-analysis of controlled trials (MacLennan, Lester, & Moore, 2001), a single available controlled trial of 20 mg ethinyl estradiol with progestin in an oral contraceptive did not significantly improve VMS in symptomatic perimenopausal women with heavy flow (Casper et al., 1997). Higher estrogen-related symptoms other than abnormal flow (premenstrual mood changes, breast tenderness and weight gain) were mentioned by 18 percent of HCP. About 25 percent of HCP interviews mentioned decreased libido and vaginal dryness as management concerns in perimenopause. These are more commonly understood to occur in women a year beyond their final period, although they are also reported in perimenopause (Gold et al., 2000). Mechanism for these is not clear in perimenopause when estrogen levels are higher (Santoro et al., 1996; Prior, 1998b) and testosterone levels are unchanged (Burger et al., 1995). Given lack of a pathophysiological understanding, it is no wonder that treatment for low sexual interest or vaginal discomfort is problematic for HCP. Although only 34 percent of these HCP interviews identified menstrual cycle and flow problems as difficult to manage in perimenopause, another practice survey found that 51 percent of women ages 40-44 and 42 percent ages 45-49 who reported seeing their practitioner for "menopause" had irregular or heavy flow as a problem (Barlow et al., 1991).

Vasomotor symptoms and sleep problems were mentioned more frequently in interviews with women than with men HCP. We can only speculate that this might be because perimenopausal women didn't feel as comfortable discussing these issues with men HCP, because women HCP could empathize and thus the issues were more prominent for them, or for unknown reasons. These data, however, reinforce the need for a gender lens in any women's health research (1984).

This survey certainly identifies the needs that HCP feel for safe and effective, evidence-based therapies for perimenopause management. That these HCP management concerns are highly variable from month to month suggests pleomorphic issues that perimenopausal women may experience (Prior, 1998b), or may simply indicate the variability in symptoms of the last patients these HCP saw. As one woman HCP complained ruefully, "My biggest problem with perimenopausal women's concerns is their expectation that I can fix it!"

Part 2: The Pilot Perimenopause Experiences Project

The clinical and geographical context in which this pilot field study began is a province in Canada with a population of about 4.5 million people and a southern, urban concentration of both population and specialist physicians. Few endocrinologists specialize in issues related to perimenopause—gynecologists are considered experts in women's reproduction, but their training is surgical. Current gynecology texts do not mention, define nor provide research evidence about perimenopause, but rather concentrate on (post)menopause. Gynecology referral for heavy flow, hot flushes or mood swings commonly leads to therapy with oral contraceptives or estrogen (Hemminki et al., 1993), and when these therapies fail, to hysterectomy. Hysterectomy is costly both for women (in life-disruption and lost productivity) and for the publicly funded universal Canadian health care system that is currently under stress. Perimenopausal high estrogen levels, in addition to causing heavy flow (Moen et al., 2004), amplify the social stress (Kirschbaum et al., 1996; Kirschbaum et al., 1996) of changing reproductive status in a culture that places value on women's youth and beauty (Page, 1994).

Having applied to perform a randomized controlled trial and not achieving funding, few research options to learn the most effective and safe therapy for symptomatic perimenopausal women were available to us. However, a donor presented

CeMCOR with the opportunity to start this field pilot study of a long distance perimenopause consultation to HCP and women. Although most telehealth projects include significant technological investment (Schlachta-Fairchild, 2001), we elected to first establish the effectiveness of long distance intervention before seeking financial support for major technology utilization.

A one-year pilot study began in 2003 to provide long distance endocrinology consultation to women and HCP in Victoria by a clinician-scientist in Vancouver who had clinical, research and personal experience in perimenopause (Prior, 1998a). The mature objectives of this project were: 1) To determine the feasibility of perimenopausal long distance consultation; 2) To determine whether the consultation decreased perimenopausal interference with each woman's activities; and 3) To determine whether the long distance consultation improved HCP self-assessed competence in management of symptomatic perimenopausal women.

The purposes of the second section of this paper are to describe the design, practical organization and baseline data on women and HCP who joined this pilot field study.

Methods

This feasibility project was conducted in partnership with the James Bay Community Project (JBCP) in Victoria. James Bay is a residential neighborhood (75% rental housing) of 11,000 within the small city of Victoria in proximity to the city centre and the provincial legislature. The JBCP that began in 1971 provides a wide range of community services (pre-school, adolescent, seniors' programmes, and a lending library) as well as a primary care clinic. A Community Advisory Council was formed from committed local women (including both a participant and a HCP representative), the research nurse (when hired) and researchers from Vancouver. This group initially met monthly and then quarterly. A local research nurse coordinator was hired, and recruitment of HCP and their referred patients started in June 2003 following ethics approvals at the University of British Columbia.

HCP were recruited to the project in two ways, through an initial letter containing an informational brochure followed by a personal meeting with the nurse, or because symptomatic patients requested their participation. Each participating woman required a

referring HCP because the primary responsibility for her health care and prescriptions remained with her HCP—the distance consultant never personally interviewed nor examined her.

Data (described below) were collected using paper forms that were photocopied and sent by postal mail or collected in person during quarterly visits by the Vancouver researchers. Consultation letters to HCP and woman participants were sent as email attachments in password-encrypted zip files to the nurse coordinator who printed and delivered them in Victoria.

The timeline for HCP participants in the project is shown in Figure 2A1. HCP who signed consent were interviewed at baseline by telephone or in person by the consultant. The interview used a structured format to assess the problems HCP have in managing perimenopausal women (part one of this paper), and their approach to two clinical scenarios. Part way through the pilot study we began asking HCP to rate their clinical competence in the management of highly symptomatic perimenopausal women using a 1-10 graphical rating scale (Figure 3A1). Each HCP completed a referral letter for each woman that included, as well as identifying information, major problems for which they sought advice, a brief past, social and allergy, medical history, and a list of all medications. In addition they assessed each woman's degree of social support. They were specifically invited to refer only symptomatic perimenopausal patients. To be eligible, these would be patients they would normally refer for specialist care. The HCP received a consultation letter concerning each referred patient about three months after she joined the study.

The timeline of the project for each symptomatic perimenopausal woman is shown in Figure 2B1. Referred women met with the nurse coordinator who provided support, answered their questions, assessed their symptoms and suitability and obtained consent. Each woman was taught to record the Daily Perimenopause Diary© (the Diary)(Hale et al., 2003) by viewing an instructional videotape (Prior, 1999). The Diary incorporates quantitative basal temperature recording, which each woman recorded on awakening—the data were analyzed quantitatively using validated least squares methods (Prior, Vigna, Schulzer, Hall, & Bonen, 1990) to provide ovulatory status and luteal phase length. Each woman's day-to-day experiences, cycle information and basal temperature on the Diary provided primary information needed by the distant consultant.

The nurse also measured each participant's height without shoes at full inspiration, weight on a beam balance, waist circumference in centimetres, blood pressure and heart rate.

Local trained volunteers worked with each woman on an interviewer-administered questionnaire [adapted from CaMOS—(Kreiger et al., 1999)] that assessed reproductive history, diet, habits, family history and history of fracture. In addition, the volunteer and participant completed the Midlife Transitions Questionnaire (Prior, unpublished) designed to assess changes in common perimenopausal experiences over the last 3 months, her current major concern, and the degree to which mood and body perimenopausal symptoms interfere with daily life (see the Perimenopause Interference Instruments, Figure 3B1). Self-administered questionnaires, completed by each participant on her own included the Rand SF-36 quality of life instrument (Hopman et al., 2000), the Multifactorial Health Locus of Control Questionnaire (Wallston, Wallston, & DeVellis, 1978), the Restraint Scale of the Eating Behavior Questionnaire (Stunkard & Messick, 1985) and the Patient Health Questionnaire (Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000). We used this latter instrument reluctantly because of its disease focus. However we needed a validated tool to formally assess emotional problems—Patient Health Questionnaire scores were used as descriptive data, not as diagnostic of psychiatric disease. These data plus three cycles of Daily Perimenopause Diary© data were all used to provide information needed for the consultation letter.

An overview of the lines of communication in this Pilot Perimenopause Experiences Project is shown in Figure 41. Women continued to record the Daily Perimenopause Diary© for one year following entry into the study, with the nurse coordinator contacting them by telephone or e-mail approximately every three months to enquire about changes in experiences, lifestyle, personal situation and therapies. At the end of the year, each woman again met with the nurse to complete a final interviewer-administered questionnaire, complete the Perimenopausal Interference Instrument (Figure 3B1) and to repeat the scored questionnaires (Rand SF-36, Multifactorial Health Locus of Control, Eating Behavior Questionnaire and Patient Health Questionnaire). They were also provided with a questionnaire designed to obtain their qualitative evaluation of the project—this was returned anonymously.

A computer science cooperative student worked with us to develop a custom-built database to enter and organize this project's data, to score the questionnaires and to facilitate study tracking. In addition, the database provided assistance with the preparation of consultation letters, generating parallel letters in medical and lay language from a menu of choices in various domains (see samples in Appendices A and B). The draft letters were then manually edited before being sent to the nurse coordinator.

Statistical analysis of the baseline pilot data from HCP and women enrolled in the Pilot Perimenopause Experience Project was confined to descriptive measures except for the least mean square testing of basal temperature data (Prior, Vigna, Schulzer, Hall, & Bonen, 1990).

Results

Nine health care providers (eight family physicians and one nurse practitioner) referred 14 symptomatic perimenopausal women and completed the year of participation. HCP averaged 15.1 years in clinical practice. HCP for this pilot included six women and three men. There were many HCP changes during the study so that, although 15 HCP initially joined the study, one completely left clinical practice, one began to work as temporary relief in different physicians' offices and didn't follow the referred patient, and three HCP did not refer any women into the project. Three referred women were not sufficiently symptomatic, or could not keep the Diary data, and three, after understanding the requirements of the study, chose not to join. The demographic characteristics of the eligible, participating women are shown in Table 31. All but one of these completed the project—the woman dropping out developed new work and home responsibilities that prevented her completing the final questionnaires.

On the referral form, HCP identified issues for which they sought consultation—on average there were 3.1 ± 1.5 such problems for each woman. In order, from most to least common, they were: breast tenderness, mood, irregular periods, hot flushes, heavy flow, night sweats, low libido, dysmenorrhea, fatigue, insomnia, anxiety, vaginal dryness, dysparunia, recurrent vaginal irritations, headaches, dizziness and spotting.

Referred women were asked to identify a single primary concern from a list of three; half of the participating women identified hot flushes and night sweats as their primary problem. Twenty-nine percent reported heavy or long flow and only 14 percent

primarily complained of breast soreness. Their baseline Perimenopausal Interference Instrument (Figure 3B1) scores were: Body Interference 5.96 ± 2.08 (range 2-9) and Mood Interference 3.96 ± 3.10 (range 0-9).

Referred women were in different phases of perimenopause (Figure 51) (Prior, 2002) fairly evenly distributed across the Phases. One third had regular cycles (Perimenopause Phases A & B), half had irregular cycles (Phase C), and the remainder had skipped and infrequent cycles (in Phases D and E).

The repeatability of HCP self-assessed clinical perimenopausal competence (Figure 3A1) was evaluated in a convenience sample of 16 HCP that included only two of the nine from this pilot (because this tool became available after start of this study). Self-assessed HCP competence was repeatable over a period of one to three months ($r = 0.77$ [n=16], $t15 = 4.67$; $p < 0.001$; mean = 6.7, range 4 to 9). Self-assessed clinical competence tended to relate to the number of symptomatic perimenopausal women each HCP reported evaluating each week ($r = 0.34$) but was not correlated with years of medical practice ($r = 0.02$).

The repeatability of the Perimenopausal Interference Instrument was also assessed by two measurements in eight women approximately 12 weeks apart. Because of the potential for different phases of the menstrual cycle to cause different experiences, the second assessment was in the same menstrual cycle phase as much as possible. The body interference score was poorly repeatable ($r = 0.520$, $P = 0.231$), but the mood interference score was stable over time ($r = 0.821$, $P = 0.023$).

Baseline Patient Health Questionnaire scores indicated that the majority of women (57%) fit into at least one diagnostic category (1.3 ± 1.3). Further, for those women with any classification, the average number of different ones was 2.3 ± 0.9 per woman. The most common assessments were somatoform disturbance (29%), major depressive symptoms (29%), anxiety disturbances (21%), and panic disorder (14%).

The Multidimensional Health Locus of Control (MHLOC) questionnaire results indicated that all women had internal Health Locus of Control as their highest scoring attitude. A breakdown of all women's health locus of control scores (mean ± SEM) showed the following distribution: powerful others (11.3 ± 4.5), internal (27.6 ± 3.6) and chance (13.1 ± 3.8).

Finally, HCP, although feedback is not yet complete, were enthusiastic about what they learned about their patient(s) and perimenopause from the consultation letter(s). A typical (anonymized) HCP consultation letter is in Appendix A1. Despite this, preliminary follow up suggests that few HCP have followed the consultant's suggestions specifically about treatment with oral micronized progesterone therapy. Symptomatic perimenopausal women reported relief after viewing the Puzzle of Perimenopause video (Prior, 1999), and learning to keep a Daily Perimenopause Diary (Hale et al., 2003) perhaps because they had some tools with which to learn about their experiences. They also reported being happy to receive their letter from the consultant. (See a sample woman's letter without identifying information, in Appendix B1). This pilot project also demonstrated that informative and insightful distance perimenopausal endocrinology consultation was possible when extensive, multi-modal data were obtained through women's Daily Perimenopause Diaries, HCP referrals, interviewer- and self-administered questionnaires, and the simple physical assessments by a nurse coordinator.

Discussion

This Pilot Perimenopause Experiences Project field study of distance medical consultations to HCP and their highly symptomatic perimenopausal women patients showed that such consultations were feasible for an experienced endocrinologist to provide. This strategy was ethically possible because all patient care and prescription writing responsibility remained with the local HCP. This pilot also showed that women and HCP were willing to participate. It represented an initial practical, woman-centred approach to deal with the confusion about the hormonal changes, time course, and lack of evidence-based therapy for symptomatic perimenopausal women. Further, by educating HCP about their own patients, each could learn within the context of her/his clinical practice and thus build capacity for potentially improved perimenopausal care.

Perimenopausal women referred into this project tended to be highly educated, with a strong internal health locus of control. This may reflect the judgment of the referring HCP about which patients would respond best to the project, or may be a function of self-selection by the women who were offered the project by their care providers. One-third of the women were referred in Phases A and B of perimenopause (Prior, 2002) and prior to any changes in menstrual cycles—these women would be

dismissed as in the "late reproductive stage" and thus not yet in perimenopause according to the most current consensus (Soules et al., 2001).

The Patient Health Questionnaire was used to help identify emotional issues for women in the study. Somewhat surprisingly, the questionnaire identified psychiatric diagnoses in over half of the women, predominantly with somatoform, depressive, and anxiety related problems. It is likely that the intensity of the hormonal changes amplified socio-cultural stresses and thus unmasked underlying personal traits. This is congruent with the fact that mood problems were identified most commonly by HCP as difficult to treat (part one). The only way to determine whether the issues identified by the Patient Health Questionnaire are truly psychiatric diagnoses would be to perform a within-woman longitudinal study that would assess whether these diagnoses changed when each woman became less symptomatic or became menopausal. This longitudinal study is planned.

Although we are still obtaining formal feedback from women and HCP, an interim analysis of eight women's results showed improvement in the Perimenopause Interference Instrument's mood domain (Figure 3B1). Until a randomized controlled trial against usual care is performed, it is not possible to know whether or not this improvement is from increased information, self-learning through Diary-keeping, the support from the nurse coordinator and interviewers (as provided to all women in the planned randomized controlled trial) or is from the distance consultation itself (the randomized portion of the study).

This pilot has also revealed a number of disadvantages within this innovative field project. The primary one is that the participation is time-consuming for perimenopausal women who are commonly already under time stress. Another obstacle to implementation of a full project is that assessment of the data and production of the consultation letters is demanding—this is onerous for a volunteer specialist, especially because she does not have the satisfaction of personal interaction with each woman and each HCP. If the benefits for women arise primarily from interaction with the nurse coordinator, such a service would be possible to implement as part of local health care delivery. It also remains to be seen whether the HCP gained in clinical competence from the consultation on their symptomatic perimenopausal patient(s). Finally, lack of availability of HCP, flux in the clinical practice environment and the stresses for HCP of being on the front line for

health care, all mean that women and projects like this encounter marked changes even within one year.

To date, only one specialist has been involved in the project. Implementing this project on a larger scale would need to incorporate training to expand the pool of distance consultants. The project was greatly assisted by the experience of the nurse coordinator who had worked for 25 years as a nurse in a remote region of the province. The consultant also drew on her experience supervising distance medical service through Community Health Aids in remote Alaska, as well as her practical clinical consultation experience with about 600 of the most symptomatic perimenopausal women in the region.

If this project is deemed successful when the final data are in, it would be important to perform a randomized controlled trial of the distance consultation compared with usual care and add an objective outcome of HCP visits during the year before and the year of consultation. That planned trial would be organized by randomization at the level of the HCP and delay of the consultation letter until that usual care HCP and her patient have completed the study. Should a randomized controlled trial prove successful, grant requests for public health funding for wider, rural application of distance perimenopausal consultation could proceed.

Summary

This narrative and pilot research describe the intricate and complex connections between science and practice. Here the personal becomes science, which becomes medical politics played out on a stage including medical publications, harried primary care physicians and nurses, academic centres and communities with their own demographics and clinical characteristics. This preliminary work demonstrates that the new science about perimenopause hormonal changes can become practical and helpful for health care providers and for women struggling to deal with hormonal chaos as well as the demands of their daily lives.

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Tables, figures and Appendices:

Table 1: List of the eleven major categories of perimenopausal concerns identified by health care provider (HCP) interviews and detail of the individual issues included under each category

Category	Category Name	HCP individual issues included in each category
1	Mood symptoms	mood problems, mood swings, emotional lability, anxiety, depression
2	Sleep disturbances	sleep troubles, insomnia, fatigue, dizzy
3	Vasomotor symptoms (VMS)	hot flushes/ hot flashes, night sweats, vasomotor symptoms
4	Menstrual cycles	irregular cycles, excessive bleeding, menorrhagia, spotting
5	Bone health	bone health, osteoporosis, bone density tests
6	Hormone therapy	questions about progesterone, estrogen, HRT, alternatives to hormones
7	Sexual disturbances	sexual dysfunction, low sex interest, declining libido, pain on intercourse
8	Pain	headache, joint pain, myalgia
9	Stress	life stress, coping, memory

10	High estrogen signs	PMS, breast tenderness, weight gain
11	Cancer risks	breast cancer, endometrial cancer worries

Table 2: Results of the test-retest data from 16 health care providers, showing the reproducibility of their concerns about perimenopausal management.

	Number of times the same concern about perimenopause was mentioned by a health care provider (HCP) on test-retest 11 ± 1 (SEM) weeks apart.			
Repeat Concerns	**None**	**One**	**Two**	**Three**
Number of HCP	4	4	7	1
Percentage of all HCP (%)	25	25	44	6

Table 3. Demographic characteristics of the women referred into the Pilot Perimenopause Experiences Project (n=14). Values are mean ± standard error.

Variable	**Mean ± SE**
Age (years)	49.1 ± 3.1
BMI	27.8 ± 5.7
Waist circumference	82.7 ± 12.8 cm (n=13)
Education:	
Some high school	1 (7%)
high school ± some higher education	4 (29%)
university degree	9 (64%)

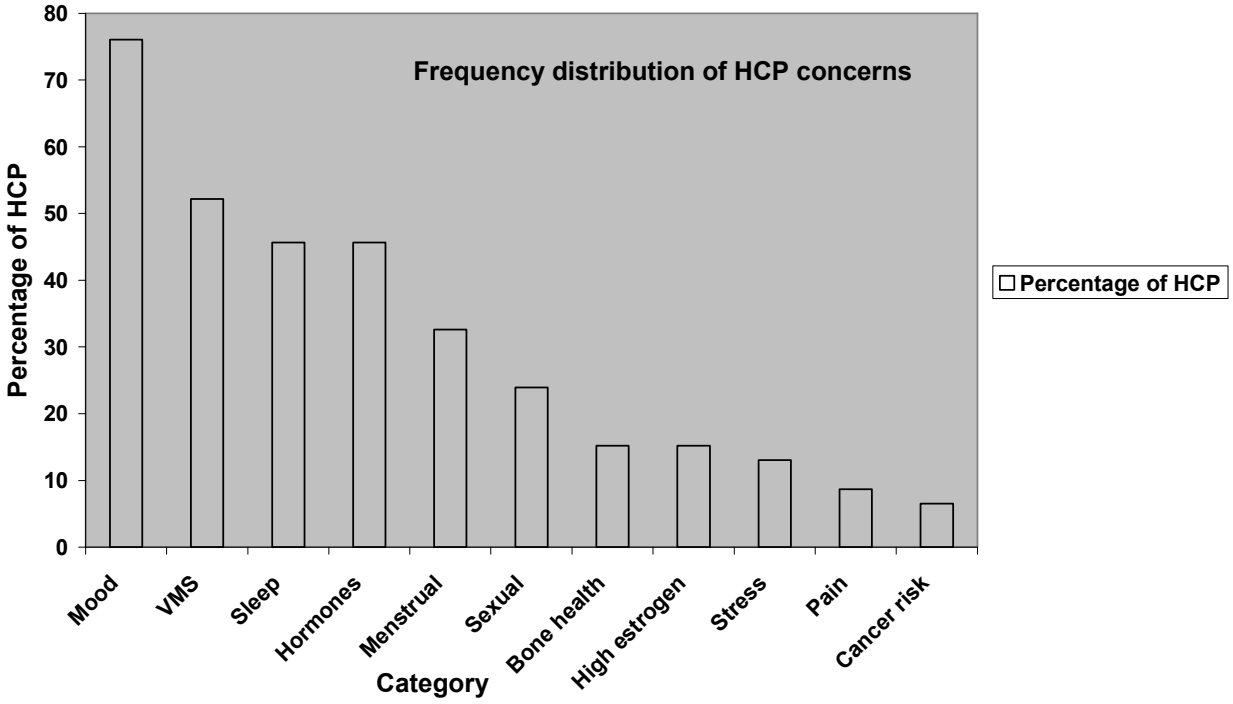
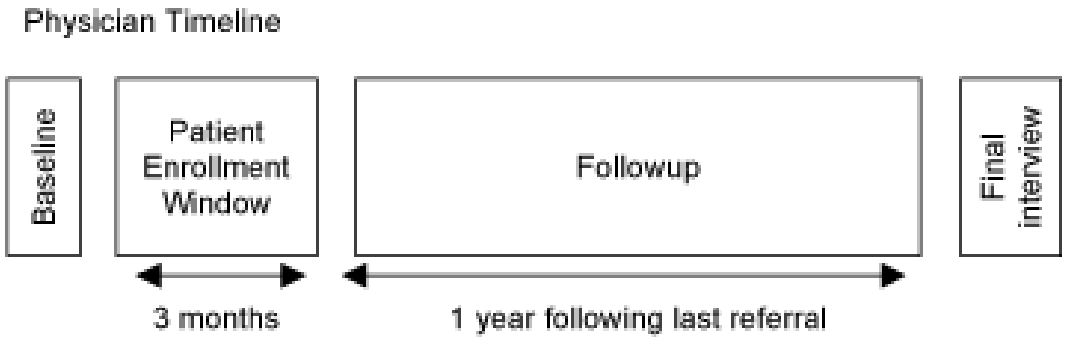


Figure 1: This frequency distribution graph shows the percentage of primary health care providers (family or general physicians and nurse clinicians, HCP) who identified each of the major eleven categories of perimenopausal concerns as a personal diagnostic or management issue.

Figure 2. Study timeline for health care providers (Physician/Nurse Clinician) **(A)** and referred women (Participant) **(B)** during the Pilot Perimenopause Experiences Project.

A.



B.

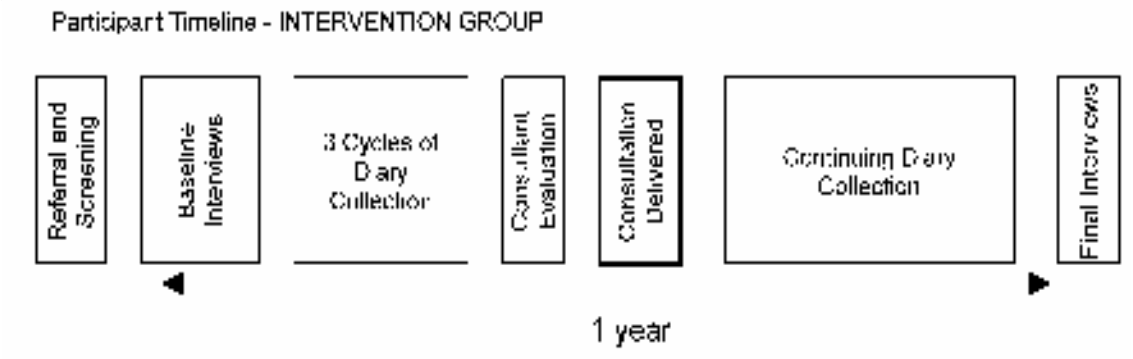


Figure 3:

A: Health Care Provider's self-assessed Clinical Competence in evaluation and management of highly symptomatic perimenopausal women

Visualize a line from 0 to 10 where 0 means very low and 10 means very high competence in the clinical assessment and care of highly symptomatic women in perimenopause. Where on this 0 to 10 line would you consider you lie?

0 1 2 3 4 5 6 7 8 9 10

Very low competence **Very high competence**

B: Perimenopausal Interference Instruments

During the past 3 months have any of the **body changes** of perimenopause interfered with your usual activities?

0 1 2 3 4 5 6 7 8 9 10

No interference **Extreme Interference**

During the past 3 months have any of the **mood changes** of perimenopause interfered with your usual activities?

0 1 2 3 4 5 6 7 8 9 10

No interference **Extreme Interference**

Figure 4. Health care delivery model for the Pilot Perimenopause Experiences Project. A local research nurse coordinates all communications between the specialist consultant and the participating primary health care providers and the referred perimenopausal women. Where required, telephone conversations between the primary HCP and the specialist consultant have been helpful.

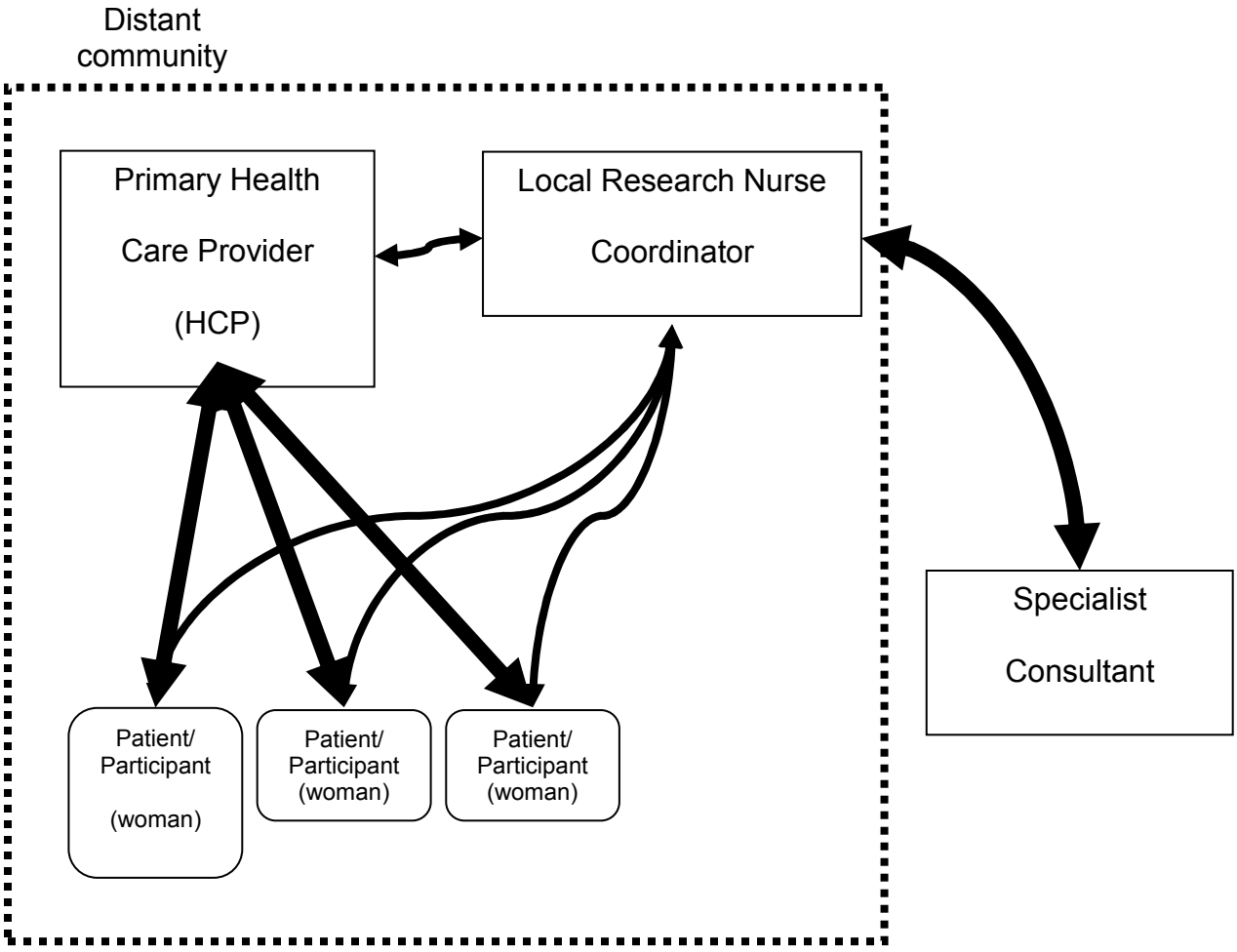
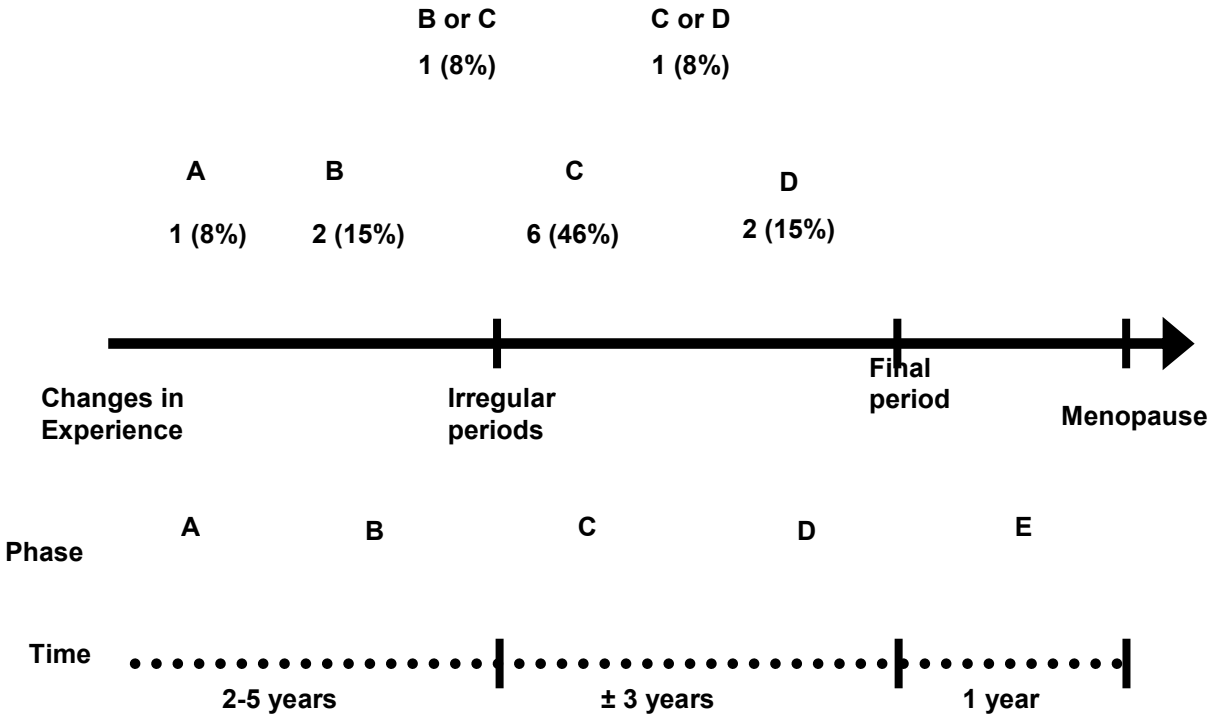


Figure 5. Distribution of referred women across the five Phases of Perimenopause (Prior, 2002).



Appendix A—Sample letter to Health Care Provider:

Dear Dr. _____

Re: _____

Thank you for referring _____ to the Perimenopause Experiences Project study. After reviewing your referral letter, three cycles of Daily Perimenopause Diary© data, her questionnaires and physical examination results, my impressions are the following:

1. Perimenopause Phase B—this is the second of five phases of the perimenopause and is characterized by regular cycles but high estrogen levels
2. High estrogen levels related to #1
3. Mastalgia related to #1 and #2
4. Past history of menorrhagia related to #1 and #2
5. Past Endometrial Ablation Surgery related to #1, #2 and #4
6. Anxiety related to #1 and #2
7. Sleep disturbances related to #1 and #6
8. Major life stresses—in particular related to knee injury and inability to do many things she previously did
9. She has a history compatible with anovulatory androgen excess (commonly called PCOS). That, in my experience, often presents in perimenopause with heavy flow. Women with this history are at increased risk for diabetes, obesity, endometrial cancer and hypertension as well as for symptoms and signs of androgen excess.

My suggestions and plans are:

1. I think that she would benefit from cyclic oral micronized progesterone (OMP, Prometrium®) therapy. The dose is 300 mg at bedtime days 14-27 of the cycle. This will not only help with breast tenderness that occurs before flow but will also improve her anxiety symptoms, help sleep and decrease her risks for endometrial cancer. (See Cyclic Progesterone Therapy on our website: www.cemcor.ubc.ca).
2. From her questionnaires it appears that she has quite severe limitations related to her past knee injury. She undoubtedly needs strengthening of the medial quadriceps and the help of a physiotherapist.
3. She needs help finding an appropriate support group or a counselor who will assist her to not feel isolated during the complex and disturbing changes of perimenopause.
4. She is taking a very low dose of thyroid hormone. Because of the complexity of symptoms in perimenopause it is very important to confirm that she needs thyroid hormone and that the dose of thyroid is appropriate for her. I suggest ordering a TSH level. It should ideally be kept between levels of 1 and 3.
5. For anxiety and mood symptoms I suggest that she needs to do some kind of exercise. The goal would be a brisk walk (or something else) at least 30 minutes a day. This has been shown to help depression, definitely helps bone and will probably help with sleep. However, at present, given her knee pain, a stationary bicycle, or swimming or something active that is not hard on her knee would need to be substituted. She may also benefit from taking glucosamine sulfate (1500 mg/d).
6. Increased calcium from diet or supplements has been shown to help premenstrual symptoms. Along with a multiple vitamin providing 400 IU of Vitamin D it will also have positive effects on bone in perimenopause.

7. I suggest that she gradually discontinue and stop DHEAS. It has androgenic effects and there is no evidence it is of benefit for someone with intact adrenal glands and ovaries.
8. I would check her weight and blood pressure regularly because should she have mild anovulatory androgen excess, perimenopause can make the risks for insulin resistance and vascular disease increase. Should she wish something to decrease facial hair or prevent head hair loss, spironolactone in a dose of 100 mg/day is very helpful. It is a direct and effective anti-androgen but will not decrease blood pressure in someone in whom it is normal.

In summary, she is a previously well woman of 46 who reports a lot of disability related to her past knee ligament injury, who is working at home and socially isolated as well as experiencing anxiety, panic attacks, and sore breasts in early perimenopause.
I hope this is helpful to you and to her. I look forward to following _____ with you. I will review the further diaries and updates related to her over the coming months and convey further suggestions to you through the nurse coordinator, _____.
Please feel free to contact me if you have any questions or concerns.
Sincerely,

Appendix B—Consultation letter to symptomatic perimenopausal woman

Dear _____,
Thank you for joining the Perimenopause Experiences Project. After reviewing Dr. ___'s referral letter, all of the questionnaires that you completed, your physical examination results and your three cycles of Daily Perimenopause Diary© data, I've come to the following ideas about what is going on with you:
First of all, I believe that you are in Perimenopause Phase B. This is a time of regular cycles with higher estrogen levels and often lower progesterone levels. Often flow is heavier or may even come too early (before 21 days). For some women, this is the worst time for sore breasts that can stay sore all month. By the end of this phase about 25% of women will have had one or more night sweats. Often these are regular and just before and during flow.
We don't really know how long this phase lasts because most experts don't call it 'perimenopause' until a woman has skipped periods. But it is really part of perimenopause because our experiences change and our hormones have already changed.
You are experiencing high estrogen levels related to perimenopause and these are the major reason for your breast tenderness. Although too little progesterone can also contribute to breast tenderness, in your case all three of your cycles were normal in progesterone level and the length of the progesterone time (luteal phase) in the cycle. However, although normal, your progesterone level is not sufficiently high to counterbalance the effects of your very high estrogen levels. The good news with breast tenderness is that it gets better as you approach and finally become menopausal!
I see that you had heavy flow for which you tried MinEstrin for seven cycles without relief. I'm glad to see that you have had improvement from the Endometrial Ablation Surgery you had. I'm also glad that you are still getting a little spotting because having some flow helps to orient us in perimenopause.
Anxiety appears to be a big problem for you and is a very common symptom in perimenopause. It is made worse because high estrogen levels amplify the stress hormone responses to usual life stresses. It is also made worse because you are presently unable to exercise. Exercise, relaxation, support and some progesterone to help with the high estrogen will all make anxiety symptoms (like racing heart beat, chest pain, trouble falling asleep and panic feelings) better.
I've suggested to Dr. _____ that she start you on cyclic progesterone (Prometrium) therapy in a dose of 300 mg at bedtime on days 14-27 of your cycle. That will help with all the things that are worse premenstrually (breast tenderness, fluid retention, mood changes) and will help you sleep. You can go to the Centre for Menstrual Cycle and Ovulation Research website www.cemcor.ubc.ca and find a handout called "Cyclic Progesterone Therapy."
It appears that you are dealing with major life stresses related to your knee injury and its interference with your daily life and activity. I have suggested to your doctor that she refer you for physiotherapy and help in strengthening the muscle that is always weak (medial quadriceps) when knees hurt. You need to try to get back to some easy walking, using a rebounder, a stationary bicycle or swimming. You may also find that taking glucosamine sulfate (500 mg three times a day) will be helpful for you.
You sound like you have a history of unwanted hair or acne, and I noted that you are now mentioning worry about head hair loss. Women with this history are at increased risk for diabetes and often develop heavy flow in perimenopause. If blood pressure becomes a

problem (it is present in your family history), a medication called spironolactone will help with that and also make the hair changes better.
I also think it is a good idea for you to find a perimenopause support group or a counselor so you don't feel so all alone during this confusing time.
I've suggested that you gradually discontinue and stop DHEAS. It is a male hormone and a stress hormone that can make things like facial hair and head hair loss worse.
I asked Dr. _____ to order a TSH test to be sure that the dose of thyroid you are taking is right for you. Too much can cause anxiety and jittery feelings and make things worse.
Increasing calcium to between 1500 and 2000 mg a day (from food and if needed from calcium pills) will also help with premenstrual symptoms and with anxiety. Your body can only use about 500 mg at a time, so spread it out during the day for best results. Along with a multiple vitamin pill a day, calcium will also help to prevent the bone loss that is normal in the later stages of perimenopause.
In summary, you are a basically healthy 46-year old woman who is coping with early perimenopause and a bum knee preventing you from doing lots of things. I have faith that cyclic progesterone therapy will help with sleep, sore breasts and over time you will feel much better. As you learn what is going on in perimenopause, get some support and can exercise more, you'll start feeling like your old self again.
I look forward to following you over this year. <the nurse coordinator> will contact you to review things every few months and will send your diaries to me. I'll make further suggestions to your doctor and <the nurse coordinator>.
Sincerely,